SENSORS FOR DIABETES: GLUCOSE BIOSENSORS BY USING DIFFERENT NEWER TECHNIQUES: A REVIEW

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ABSTRACT

Diabetes lasts a life time. Poor control blood glucose (sugar) damages the body. Good control of blood glucose can delay and even prevent diabetic complications. Diabetes mellitus is the most common endocrine disorder of carbohydrate metabolism.Worldwide, it is a leading cause of morbidity and mortality and a major health problem for most developed societies. The prevalence of diabetes continues to increase.

The crude estimated prevalence of -diabetes in adults in the United States (US) has been reported to be 9.6% (20.4 million) in 2003-2006.

Previously testing of blood sugar level was a tedious process but now a day's Glucose biosensors have evolved to be more reliable, rapid, and accurate and are also more compact and easy to use. The majority of the current glucose biosensors are of the electrochemical type, because of their better sensitivity, reproducibility, and easy maintenance as well as their low cost.

The basic concept of the glucose biosensor is based on the fact that the immobilized GOx catalyzes the oxidation of β-D-glucose by molecular oxygen producing gluconic acid and hydrogen peroxide. Research for advanced technologies, including electrodes, membrane, immobilization strategies, and nanomaterials continue to be performed. Despite the impressive advances in glucose biosensor technology, there are still several challenges related to the achievement of reliable glucose monitoring.

Keywords: Diabetes mellitus; Glucose biosensor; point-of-care testing; performance; Selfmonitoring of blood glucose.

INTRODUCTION

The term *biosensor* has been variously applied to a number of devices either used to monitor living systems or incorporating biotic elements. A recent IUPAC committee has been trying to unravel a literature that, at one time or another, has used the term to describe a thermometer,a mass spectrometer, *daphnia* in pond water, electrophysiology equipment, chemical labels for imaging and ion-selective electrodes. The consensus, however, is that the term should be reserved for use in its modern context of a sensor incorporating a biological element such as an enzyme, antibody, nucleic acid, microorganism or cell; this decision is readily endorsed by a cursory examination of a data base such as Chemabs. A biosensor can be defined as a "compact analytical device or unit incorporating a biological or biologically derived sensitive recognition element integrated or associated with a physio-chemical transducer". The diagnosis and management of diabetes mellitus requires a tight monitoring of blood glucose levels. Electrochemical biosensors for glucose play a leading role in this direction. This review discusses the principles of operation of electrochemical glucose biosensors, examines their history, discusses recent developments and current status surveys major strategies for enhancing their performance, and outlines key challenges and opportunities in their further development and use.

Biosenser determines the presence and concentration of a specific substance in any test solution.

There are many promising systems on the horizon, but the only commercially-deployed biosensors are glucose monitors (~$4B). 3 main

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types:

Single Use: Disposable sensing material, often "static" measurement. Cheap and portable, but low sensitivity and accuracy.

Intermittent Use: Often use hydrodynamics – generally much better performance from sensing a moving fluid. Its still a challenge to move these out of the lab and onto a chip.

Continuous (In Vivo) Sensors: Very economical, but very hard to calibrate and may suffer from unknown amount of drift.

HISTORY OF BIOSENSOR

Father of the Biosensor

Leland C. Clark Jr. (1918–2005) was an American biochemist born in Rochester, New York He is most well known as the inventor of the Clark electrode, a device used for measuring oxygen in blood, water and other liquids, Clark is considered the "Father of Biosensors", and the modern-day glucose sensor used daily by millions of diabetics is based on his research. The history of glucose enzyme electrodes began in 1962 with the development of the first device by Clark and Lyons of the Cincinnati Children's Hospital.

First glucose enzyme electrode relied on a thin layer of GOx entrapped over an oxygen electrode via a semipermeable dialysis membrane. Measurements were made based on the monitoring of the oxygen consumed by the enzyme-catalyzed reaction.

$$\text{Glucose} + O_2 \xrightarrow{\text{glusoce oxidase}} \text{Gluconic acid} + H_2O_2$$

A negative potential was applied to the platinum cathode for a reductive detection of the oxygen consumption.

$$O_2 + 4H^+ + 4\,e^- \rightarrow 2H_2O$$

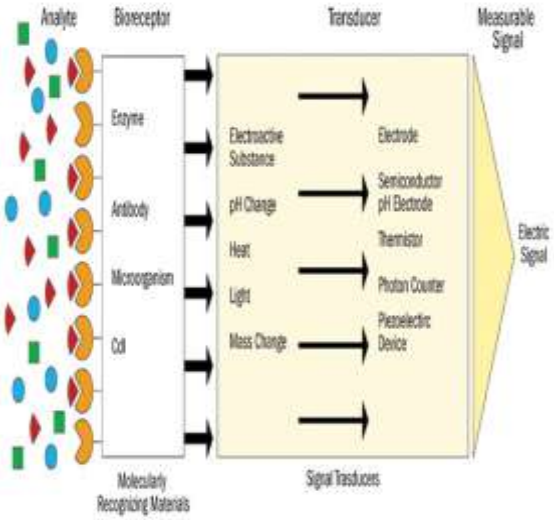
History of Biosensors

- 1916- First report on immobilization of proteins : adsorption of invertase on activated charcoal
- 1922 -First glass pH electrode
- 1956- Clark published his definitive paper on the oxygen electrode.
- 1962- First description of a biosensor: an amperometric enzyme electrodre for glucose (Clark)
- 1969-Guilbault and Montalvo – First potentiometric biosensor:urease immobilized on an ammonia electrode to detect urea
- 1970-Bergveld –ion selective Field Effect Transistor (ISFET)
- 1975 -Lubbers and Opitz described a fibre-optic sensor with immobilised indicator to measure carbon dioxide or oxygen.
- 1975-First commercial biosensor (Yellow springs Instruments glucose biosensor)
- 1975-First microbe based biosensor, First immunosensor
- 1976-First bedside artificial pancreas (Miles)
- 1980-First fibre optic pH sensor for in vivo blood gases (Peterson)
- 1982-First fibre optic-based biosensor for glucose
- 1983-First surface plasmon resonance (SPR) immunosensor
- 1984-First mediated amperometric biosensor: ferrocene used with glucose oxidase for glucose detection
- 1987-Blood-glucose biosensor launched by MediSense ExacTech
- 1990-SPR based biosensor by Pharmacia BIACore
- 1992-Hand held blood biosensor by i-STAT
- 1996-Launching of Glucocard
- 1998-Blood glucose biosensor launch by LifeScan FastTake
- 1998-Roche Diagnostics by Merger of Roche and Boehringer mannheim

- Current Quantom dots, nanoparicles, nanowire, nanotube, etc.

Basic Principles of Glucose Biosensors

There are three main parts of a biosensor: (i) the biological recognition elements that differentiate the target molecules in the presence of various chemicals, (ii) a transducer that converts the biorecognition event into a measurable signal, and (iii) a signal processing system that converts the signal into a readable form. The molecular recognition elements include receptors, enzymes, antibodies, nucleic acids, microorganisms and lectins.



The five principal transducer classes are electrochemical, optical, thermometric, piezoelectric, and magnetic.

The majority of the current glucose biosensors are of the electrochemical type, because of their better sensitivity, reproducibility, and easy maintenance as well as their low cost. Electrochemical sensors may be subdivided into potentiometric, amperometric, or conductometric types.

Enzymatic amperometric glucose biosensors are the most common devices commercially available, and have been widely studied over

the last few decades. Amperometric sensors monitor currents generated when electrons are exchanged either directly or indirectly between a biological system and an electrode.

Generally, glucose measurements are based on interactions with one of three enzymes: hexokinase, glucose oxidase (GOx) or glucose-1-dehydrogenase (GDH) . The hexokinase assay is the reference method for measuring glucose using spectrophotometry in many clinical laboratories.

Glucose biosensors for SMBG are usually based on the two enzyme families, GOx and GDH. These enzymes differ in redox potentials, cofactors, turnover rate and selectivity for glucose. GOx is the standard enzyme for biosensors; it has a relatively higher selectivity for glucose. GOx is easy to obtain, cheap, and can withstand greater extremes of pH, ionic strength, and temperature than many other enzymes, thus allowing less stringent conditions during the manufacturing process and relatively relaxed storage norms for use by lay biosensor users The basic concept of the glucose biosensor is based on the fact that the immobilized GOx catalyzes the oxidation of β-D-glucose by molecular oxygen producing gluconic acid and hydrogen peroxide.

In order to work as a catalyst, GOx requires a redox cofactor—flavin adenine dinucleotide (FAD). FAD works as the initial electron acceptor and is reduced to $FADH_2$.

Glucose + GOx + FAD→ Glucolactone + GOx + FADH2

The cofactor is regenerated by reacting with oxygen, leading to the formation of hydrogen peroxides. Hydrogen peroxide is oxidized at a catalytic, classically platinum (Pt) anode. The electrode easily recognizes the number of electron transfers, and this electron flow is proportional to the number of glucose molecules present in blood.

$$H2O2 \rightarrow 2H^{+} + O2 + 2e$$

Three general strategies are used for the electrochemical sensing of glucose; by measuring oxygen consumption, by measuring the amount of hydrogen peroxide produced by the enzyme reaction or by using a diffusible or immobilized mediator to transfer the electrons from the GOx to the electrode. The number and types of GDH-based amperometric biosensors have been increasing recently. The GDH family includes GDH-pyrroquinolinequinone (PQQ) and GDH-nicotinamide-adenine dinucleotide (NAD) . The enzymatic reaction of GDH is independent of the dissolved oxygen. The quinoprotein GDH recognition element uses PQQ as a cofactor.

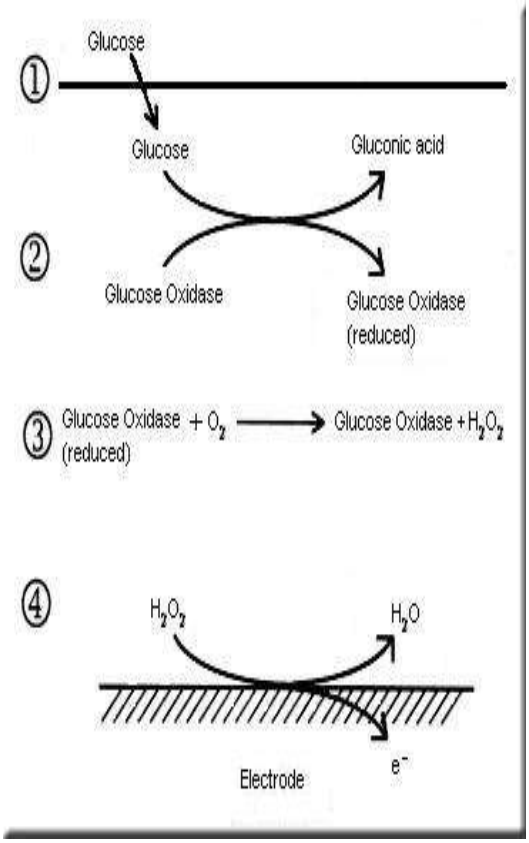
Glucose + PQQ(ox) → gluconolactone + PQQ(red)

This mechanism requires neither oxygen nor NAD+. GDH-PQQ is a particularly efficient enzyme system, with a rapid electron transfer rate, but it is relatively expensive.

GDH with NAD as a cofactor produces NADH rather than H2O2. NAD is a major electron acceptor in the oxidation of glucose, during which the nicotinamide ring of NAD+ accepts a hydrogen ion and two electrons, equivalent to a hydride ion. The reduced form of this carrier generated in this reaction is called NADH, which can be electrochemically oxidized.

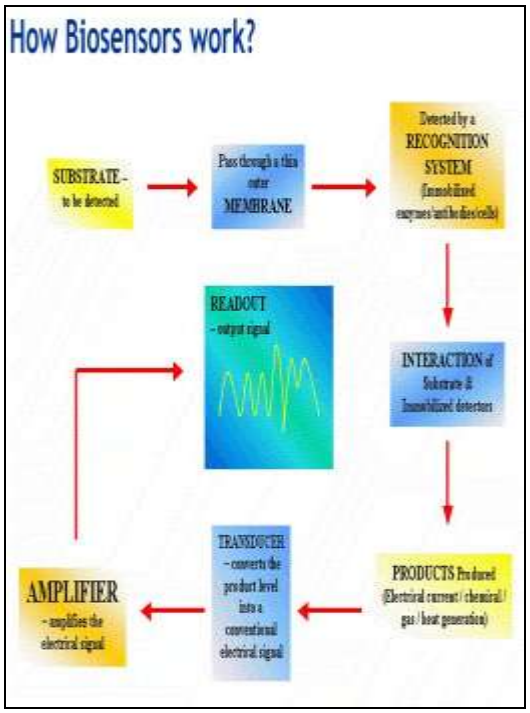
$$\text{Glucose} + NAD^+ \rightarrow \text{gluconolactone} + NADH$$

$$NADH \rightarrow NAD^+ + H^+ + 2e$$



Basic characteristics of a biosensor-

1. **Linearity** Linearity of the sensor should be high forthe detection of high substrate concentration.
2. **Sensitivity** Value of the electrode response per substrate concentration.
3. **Selectivity** Chemicals Interference must be minimised for obtaining the correct result.
4. **Response time** Time necessary for having 95% of the response



Integrated systems

Biosensor technologists strive for the simplest possible solution to measurement in complex matrices. While notable success has been achieved with individual sensors, pragmatic solutions to many problems involve the construction of a sensor system in which the carefully optimised performance of the sensor is supported by associated electronics, fluidics and separation technology. In process monitoring, for example, the process must remain inviolate while the sensor frequently requires protection from the process and its products. We have designed an integrated system comprising a rotary aseptic sampling system with flow-injection analysis incorporating a reusable, screen-printed electrode. The enzyme electrode utilised glucose oxidase immobilised in a hydrophilic gel and detected hydrogen peroxide at a catalytic electrode made of rhodinised carbon. While the enzyme electrode alone exhibited enhanced stability and interference characteristics, a complete solution of the monitoring problem demanded the optimisation of the whole system. There are increasing demands for a systems orientated approach in other sectors; environmental monitoring places demands on sensor technology that in many cases are unlikely to be met by isolated sensors, and in clinical monitoring

microdialysis offers a useful way forward for measurement *in vivo.* The sensor/sampling system biointerface is a key target for further investigation and we are using evanescent wave techniques and atomic force microscopy to further our understanding of protein interactions. Work on *in vivo* sensing systems for both glucose and lactate has confirmed the effectiveness of phospholipid copolymers in improving haemocompatability. Immunosensors offer a further general example where micro separations, using for example immuno-chromatographic methods, can be coupled with electrochemical or optical detectors to yield simple dip-stick style devices combining the speed and convenience of sensors with the specificity and sensitivity of immunoassays. The advent of micromachining makes these and other hyphenated techniques amenable to such a high degree of miniaturisation that the distinction between sensor and analytical instrument becomes hazy.

Sensitivity

Clinicians, food technologists and environmentalists all have an interest in generally increased sensitivity and limits of detection for a range of analytes. While the precise demands to meet today's requirements may be modest in these respects, few would contest the longer term benefits of reliable detection of trace amounts of various indicators, additives or contaminants. With the advent of atomic force microscopy we can consider single molecule detection in the research laboratory, but great strides have also been made with conventional sensors. Enzyme electrodes have been designed which preconcentrate the analyte of interest. We have reported a gas-phase microbiosensor for phenol, for example, in which polyphenol oxidase was immobilised in a glycerol gel on an interdigitated microelectrode array. Phenol vapour partitioned directly into the gel where it was oxidised to quinone. Signal amplification was enhanced by redox recycling of the quinone/catechol couple resulting in a sensor able to measure 30 ppb phenol. Detection limits of parts per trillion volatile organic carbons are feasible with this approach. Ultra-low detection limits are achievable with affinity sensors and electrochemical detection may be readily integrated with chromatographic techniques to yield user-friendly devices. In an alternative approach, double-stranded DNA may be used as a receptor element. "Sandwich"-type biosensors based on liquid-crystalline dispersions formed from DNA-polycation complexes may find application in the determination of a range of compounds and physical factors that affect the ability of a given polycation molecule to maintain intermolecular crosslinks between neighbouring DNA molecules. In the case of liquid-crystalline dispersions formed from DNA-protamine complexes, the lowest concentration detectable of the hydrolytic enzyme trypsin was 10-14M. Elimination of the cross links caused an increase in the distance between the DNA molecules which resulted in the appearance of an intense band in the circular dichroism spectrum and a "fingerprint" (cholesteric) texture. Work is in progress to develop mass-producible films and inexpensive instrumentation.

Stability

Arguably the most obvious disadvantage in exploiting the exquisite specificity and sensitivity of complex biological molecules is their inherent instability. Many strategies may be employed to restrain or modify the structure of biological receptors to enhance their longevity. We have recently confirmed the effectiveness of sol gels as an immobilisation matrix in an optode for glucose using simultaneous fluorescence quenching of two indicators, (2,2'-bipyridyl)ruthenium(II) chloride hexahydrate and 1-hydroxypyrene-3,6,8-trisulphonic acid. In addition to the excellent optical properties of the gel, enhanced stability of the glucose oxidase catalyst was clearly evident. Some desirable activities, however, remain beyond the reach of current technology. Methane monooxygenase is one such case where, despite reports of enhanced stability in the literature, the demands of hydrocarbon detection require stability far beyond that exhibited by the enzyme. In these cases it is valuable to resort to biomimicry to retain the essence of the biocatalytic activity, but to house this within a smaller and more robust structure. For example, we have developed a simple and rapid method for quantifying a range of toxic organohalides based on their electrocatalytic reaction with a metalloporphyrin catalyst. This approach can be used to measure Lindane and carbon tetrachloride (representative of haloalkane compounds) perchloroethylene (a typical haloalkene) 2,4D and pentachlorophenol (aromatics) and the insecticide DDT.

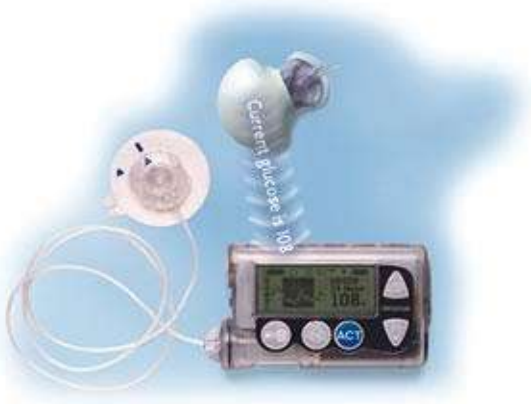
Selectivity

Improvement in the selectivity of biosensors may be sought at two levels; the interface between the transducer and the biological receptor may be made

more exclusive thus reducing interference, and new receptors can be developed with improved or new affinities. The use of mediators as a strategy to improve performance in amperometric biosensors has proved extremely popular and we have continued to explore these possibilities. A recent publication (describes the use of pyrroloquinoline quinone as a "natural" mediator, but used with glucose oxidase in an enzyme electrode for the measurement of sugar in drinks. Alternatively, electrocatalytic detection of the products of enzymatic reactions may be enhanced by the use of chemically modified electrodes such as rhodinised or hexacyanoferrate-modifie carbon. The latter method results in a Prussian Blue coating on the electrode which may then be used for amperometric detection of hydrogen peroxide at both oxidative and reductive potentials in enzyme electrodes for lactate and glucose. Arguably a more elegant solution is to seek connection of the redox centre of an enzyme to an electrode via a molecular wire. Much has been published about so called "wired" enzymes, but these papers have generally been concerned with immobilised mediators on various polymer backbones. We have sought to use molecular wires in their pure sense for long distance electron transfer effected via a single molecule with delocalised electrons. Novel heteroarene oligomers, consisting of two pyridinium groups, linked by thiophene units of variable length (thienoviologens) are promising candidates for such conducting molecular wires and may be used in conjunction with self-assembly techniques to produce an insulated electrode which transfers electrons specifically along predetermined molecular paths. This design should produce enzyme electrodes free from electrochemical interference. Advances in computational techniques now allow us to model both electron transfer reactions and receptor binding interactions with increasing accuracy. This not only enhances our understanding of the receptor/transducer interface, but allows us to consider designing new receptors based on biological molecules. To obtain improved binding ligands for use in an optical sensor for glycohemoglogin (HbA1c), a novel synthetic peptide library composed of one million L-amino acid hexapeptides was constructed from ten amino acids using combinatorial chemistry. The hexapeptide library was screened against HbA1c, HbA1b, HbAF and HbA0, and selected ligands sequenced. Individual ligands or arrays of ligands in conjunction with pattern recognition techniques will be used to design a sensor with improved selectivity.

Example of biosensors

Pregnancy test Detects the hCG protein in urine Glucose monitoring device (for diabetes patients)



First-generation of Glucose Biosensors

The first-generation glucose biosensors were based on the use of natural oxygen substrate and on the detection of the hydrogen peroxide produced. Measurements of peroxide formation have the advantage of being simpler, especially when miniature devices are being considered .However, the main problem with the first-generation of glucose biosensors was that the amperometric measurement of hydrogen peroxide required a high operation potential for high selectivity.

Second-generation of Glucose Biosensors

The abovementioned limitations of the first-generation glucose biosensors were overcome by using mediated glucose biosensors, *i.e.*, second-generation glucose sensors. The improvements were achieved by replacing oxygen with non-physiological electron acceptors, called redox mediators that were able to carry electrons from the enzyme to the surface of the working electrode. A reduced mediator is formed instead of hydrogen peroxide and then reoxidized at the electrode, providing an

amperometric signal and regenerating the oxidized form of the mediator A variety of electron mediators, such as ferrocene, ferricyanide, quinines, tetrathialfulvalene (TTF), tetracyanoquinodimethane (TCNQ), thionine, methylene blue, and methyl viologen were used to improve sensor performance.

During the 1980s, mediator-based second-generation glucose biosensors, the introduction of

commercial screen-printed strips for SMBG, and the use of modified electrodes and tailored membranes for enhancing the sensor performance were developed and implemented. The first

electrochemical blood glucose monitor for self-monitoring of diabetic patients was pen-sized and was launched in 1987 as ExacTech by Medisense Inc. It used GDH-PQQ and a ferrocene derivative .Its success led to a revolution in the health care of diabetic patients. The current operation of most commercial glucose biosensors does not differ significantly from that of the ExacTech meter. Various self-monitoring glucose biosensors are based on the use of ferrocene or ferricyanide mediators.

Third-generation of Glucose Biosensors

The third-generation glucose biosensors are reagentless and based on direct transfer between the

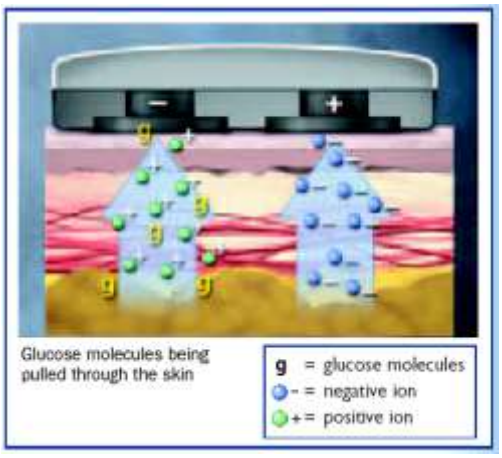
enzyme and the electrode without mediators. Instead of mediators with high toxicity, the electrode can perform direct electron transfers using organic conducting materials based on charge-transfer complexes. Therefore, third-generation glucose biosensors have led to implantable, needle-type devices for continuous *in vivo* monitoring of blood glucose. Conducting organic salts, such as tetrathiafulvalene-tetracyanoquinodimethane (TTF-TCNQ), are known to mediate the electrochemistry of pyrrole-quinolinequinone enzymes (GDH-PQQ) as well as of flavoproteins (GOx). And the absence of mediators provides the biosensors with superior selectivity. However, only a few enzymes including peroxidases have been proved to exhibit direct lectron transfer at normal electrode surfaces . Several studies for other direct electron transfer approaches on the third-generation glucose biosensors have been reported, including TTF-TCNQ that has a tree-like crystal structure, the GOx/polypyrrole system and oxidized boron-doped diamond electrodes.

Continuous Glucose Monitoring Systems (CGMS)

Two types of continuous glucose monitoring systems are currently in use - a continuous

subcutaneous glucose monitor and a continuous blood glucose monitor. However, due to surface

contamination of the electrode by proteins and coagulation factors and the risk of thromboembolism, most of the CGMSs do not measure blood glucose directly. Therefore, subcutaneously implantable needle-type electrodes measuring glucose concentrations in interstitial fluid have been developed, which reflect the blood glucose level.



Non-invasive Glucose Monitoring System

Non-invasive glucose analysis is another goal of glucose sensor technology and significant efforts have been made to achieve this goal. Optical or transdermal approaches are the most common noninvasive glucose sensing methods. The GlucoWatch Biographer, manufactured by Cygnus, Inc. (Redwood City, CA, USA), was the first transdermal glucose sensor approved by the US FDA.

This watch-like device was based on transdermal extraction of interstitial fluid by reverse iontophoresis. It never widely accepted in the market due to long warm up time, false alarm, inaccuracy, skin irritation and sweating. It was withdrawn in 2008.

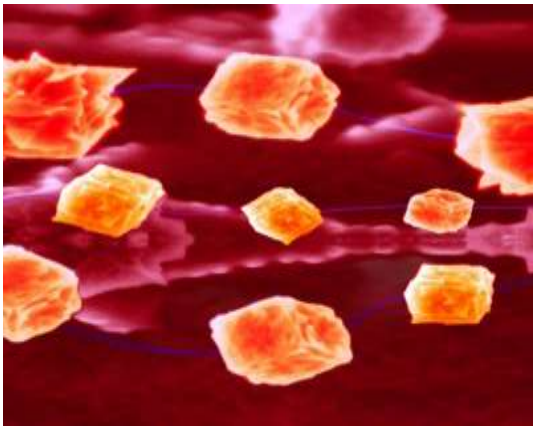
Considerable efforts have been made in the development of non-invasive glucose devices. However, reliable non-invasive glucose measuring method is still not available.

Glucose Biosensors for Pont-of-Care Testing (POCT)

Although laboratory analysis is the most accurate method for evaluating glucose levels, because of cost and time delays, POCT is widely used to determine glucose levels in the inpatient (ER/ICU/ward) and outpatient (office/home) setting. The majority of POC glucose biosensors rely on disposable, screen-printed enzyme electrode test strips. These plastic or paper strips have electrochemical cells and contain GDH-PQQ, GDH-NAD, GDH-FAD, or GOx along with a redox mediator. A test strip is first inserted into the meter, and then a small drop of capillary blood is obtained from the fingertip with a lancing device, and is applied to the test strip. Finally, a conversion factor is applied and the measurement results are typically displayed as plasma glucose equivalents according to the IFCC recommendation.

The Use of Nanomaterials in Biosensors

To date, modern materials science has reached a high degree of sophistication. As a result of continuous progress in synthesizing and controlling materials on the submicron and nanometer scales, novel advanced functional materials with tailored properties can be created. When scaled down to a nanoscale, most materials exhibit novel properties that cannot be extrapolated from their bulk behavior. The interdisciplinary boundary between materials science and biology has become a fertile ground for new scientific and technological development. For the fabrication of an efficient biosensor, the selection of substrate for dispersing the sensing material decides the sensor performance. Various kinds of nanomaterials, such as gold nanoparticles,carbon nanotubes (CNTs) ,magnetic nanoparticles and quantum dots are being gradually applied to biosensors because of their unique physical, chemical, mechanical, magnetic and optical properties, and markedly enhance the sensitivity and specificity of detection.



Caption: This image, taken with a scanning electron microscope and digitally colorized and enhanced, shows a new precise biosensor for detecting blood glucose and other biological molecules using hollow structures called single-wall carbon nanotubes anchored to gold-coated "nanocubes." The device resembles a tiny cube-shaped tetherball anchored to electronic circuitry by a nanotube about 25,000 times thinner than a human hair.

The glucose biosensor has been widely used as a clinical indicator of diabetes. Nanoscale materials such as GNPs, CNTs, magnetic nanoparticles,Pt nanoparticles [90], Quantum dots, etc. play an important role in glucose sensor performance, fibrous morphology and wrapping of PDDA over MWCNTs result in a high loading of GOx into the electrospun matrix,Pt nanoparticles could be electrodeposited on MWNTs matrix in a simple and robust way. The immobilization of glucose oxidase onto Pt/MWNTs electrode surfaces also could be carried out by chitosan-SiO2 gel. The resulting biosensors could be used to determine the glucose levels of serum samples with high sensivity.

RESULTS

Major advances have been made for enhancing the capabilities and improving the reliability of glucose measuring devices. Such intensive activity has been attributed to tremendous economic prospects and fascinating research opportunities. The success of glucose blood monitors

has stimulated considerable interest in in vitro and in vivo devices for monitoring other physiologically important compounds. Despite the impressive advances in glucose biosensors, there are still many challenges related to the achievement of tight, stable and reliable glycemic monitoring. The

development of new and improved glucose biosensors thus remains the prime focus of many researchers.

DISCUSSION

As this field enters the fifth decade of intense research we expect significant efforts coupling fundamental sciences with technological advances. Such stretching of the ingenuity of researchers will result in greatly improved electrical contact between the redox center of GOx and electrode surfaces, enhanced ‘‘genetically engineered’’ GOx, new ‘‘painless’’ in vitro

testing, advanced biocompatible membrane materials, the coupling of minimally invasive monitoring with compact insulin delivery system, new innovative approaches for noninvasive

monitoring, and miniaturized long-term implants. These, and similar developments, will greatly improve the control and management of diabetes

CONCLUSIONS

Glucose biosensors have evolved to be more reliable, rapid, and accurate and are also more compact and easy to use. Research for advanced technologies, including electrodes, membrane, immobilization strategies, and nanomaterials, continue to be performed. Despite the impressive advances in glucose biosensor technology, there are still several challenges related to the achievement of reliable glucose monitoring. The ADA recommends the accuracy of a blood glucose POC assay to be <5% of the measured value. However, many POC devices do not meet this criterion. Biosensor technology is less precise and less accurate than the methods used in central laboratories. A more systematic evaluation of the analytical performance of glucose biosensors is recommended to ensure reliable and accurate testing. Analytical requirements for suitable hospital or home POC devices include good linearity, precision, and correlation when compared to a clinical laboratory reference method as well as resistance to common interferences. The calibration of the devices and quality control should be performed on a regular basis according to the manufacturer’s instructions. User-dependent factors can also affect data quality, and by extension, treatment outcomes. The most commonly cited problems are incorrect use of the test strip, lack of quality control procedure, fingers that are not clean and dirty devices.

Accordingly, for nearly 50 years we have witnessed tremendous progress in the development of electrochemical glucose biosensors. Elegant research on new sensing concepts, coupled with numerous technological innovations, has thus opened the door to widespread applications of electrochemical glucose biosensors. Such devices account for nearly 85% of the world market of biosensors. Major fundamental and technological advances have been made for enhancing the capabilities and improving the reliability of glucose measuring devices. Such intensive activity has been attributed to the tremendous economic prospects and fascinating research opportunities associated with glucose monitoring. The success of glucose blood meters has stimulated considerable interest in in-vitro and in-vivo devices for monitoring other physiologically important compounds.

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